Ezogabine (Potiga)
National Drug Monograph
November 2014
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Ezogabine activates voltage-gated potassium channels. This leads to inhibition of hyperexcitability activity in the central nervous system (CNS). This ability to enhance the potassium channel allows seizure frequency to be reduced.
Indication(s) Under Review	Ezogabine is a potassium channel opener indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older who have responded inadequately to several alternative treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity.
Dosage Form(s) Under Review	film-coated immediate-release tablets for oral administration containing 50 mg, 200 mg, 300 mg, or 400 mg of ezogabine
REMS	☒ REMS ☐ No REMS ☒ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy Category C. North American Antiepileptic Drug (NAAED) Pregnancy Registry (for patients) at 888-233-2334

Executive Summary	
Efficacy	• The median percent change from baseline in monthly partial seizure frequency was 23% for 600 mg/day, 29% for 900 mg/day and 35% for 1200 mg/day, in comparison to 13% for placebo ($p < 0.001$ for the overall differences across all treatment arms) • Pooling the results from the three pivotal trials and all dosages investigated provides a relative risk of the responder rate of 2.14 (95% CI: 1.70–2.70; $p < 0.001$) using the LOCF method. • Although only 21.2% (114/539) of patients enrolled in RESTORE-2 and 22.6% (69/305) of patients enrolled in RESTORE-1 remained in the extension studies at 24 months, these patients experienced benefit with the addition of ezogabine. • All studies showed a statistically significant increase in withdrawal due to adverse events with ezogabine compared to placebo with rates of discontinuation due to adverse events ranging from 14.4% to 29.2% and appeared to be dose-related (25% across all three studies for ezogabine vs. 11% for placebo).
Safety	• Ezogabine can cause retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss. • Ezogabine caused urinary retention in clinical trials in approximately 2% of

	treated patients. Urologic symptoms should be carefully monitored, especially in those who have other risk factors for urinary retention. • In a single study, ezogabine produced a mean 7.7 msec QT prolongation in healthy volunteers. The QT interval should be monitored when it is prescribed with medicines known to increase QT interval and in patients with known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia. • The most common adverse reactions leading to withdrawal were dizziness (6%), confusional state (4%), fatigue and somnolence (3%). In the clinical trials, dizziness was reported in 23% of patients treated with ezogabine compared to 9% of patients on placebo. Confusional state, psychotic symptoms and hallucinations were reported more frequently in patients treated with ezogabine than in those treated with placebo in the clinical trials (9% of ezogabine participants experienced a confusional state versus 3% in the placebo group)
Other Considerations	• The Drug Enforcement Agency (DEA) has determined that ezogabine should be categorized as a schedule V controlled substance under the Controlled Substance Act. Chemically, ezogabine has demonstrated CNS depressant properties and is classified as a sedative-hypnotic.
Potential Impact	• Based on current studies ezogabine would be appropriate as add-on therapy for patients that are receiving at least one other antiepileptic for partial seizures. At this time it cannot be recommended as first-line monotherapy. • In comparison to other second and third generation antiseizure medications (topiramate, levetiracetam, and lacosamide); the reduction in overall seizure frequency (primary outcome) and responder rate (secondary outcome) versus placebo were comparable to those demonstrated in the ezogabine trials (high quality evidence)

Background

Purpose for review

Issues to be determined:

✔ Is there a need for therapeutic alternatives to used as adjunct therapy in treatment resistant epilepsy patients?
✔ Does ezogabine offer advantages to currently available alternatives?
✔ Does ezogabine offer advantages over current VANF agents?
✔ What safety issues need to be considered?
✔ Does ezogabine have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations
Topiramate	Weight loss, renal stones, acute closure in narrow angle glaucoma, hyperthermia and oligohidrosis, metabolic acidosis. May worsen pre-existing cognition issues, metabolic acidosis with concomittant metformin use.
Levetiracetam	Renal excretion--minimal interactions. Sedation, irritability, agitation, anxiety, depression
Lamotrigine	Rash (Stevens Johnson Syndrome, Toxic epidermal necrolysis) Dizziness, tremor, ataxia, headache, vivid dreams, insomnia

Carbamazepine	Consider sending HLA B*1501 test prior to initiation (Asian ancestry, cross-AED allergy), p450 inducer-Interacts with warfarin and many drugs.
Non-formulary Alternative	**Other Considerations**
Lacosamide	renal excretion--minimal interactions. AV conduction abnormalities
Eslicarbazepine	eosinophilia and systemic symptoms (DRESS) reported
Pregabalin	Avoid in pre-existing cognition issues
Vigabatrin	Requires eye exams q3months, SHARE program registration. Progressive and permanent bilateral peripheral visual constriction

Efficacy (FDA Approved Indications)

Literature Search Summary
MEDLINE and EMBASE were systematically searched using search terms retigabine and ezogabine for randomized controlled trials published from 1980 through August 17, 2013. Additionally, articles relating to pharmacology, pharmacokinetics, tolerability and interactions were examined for inclusion. Published abstracts and websites of the Food and Drug Administration and European Medication Agency were reviewed for additional relevant information. The search was limited to studies performed in humans, in adults and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Ezogabine was approved based on three double-blind high quality studies (two 16-week and one 18-week) involving 1,239 patients with inadequately controlled partial-onset seizures already receiving 1-3 antiseizure medications (AED). The studies evaluated doses from 600mg – 1200mg. In a dose-ranging study, ezogabine 900mg/day and 1200mg/day demonstrated a statistically significant reduction in the total partial seizure rate compared to placebo (-29.3% in 900mg/day arm, -35.2% in 1200mg/day arm, and -13.1% in placebo; p=0.0387 and 0.0024, respectively). These treatment groups also showed a significantly higher responder rate, defined as ≥50% reduction in 28-day rate of seizures (900mg/day: 31.6%, 1200mg/day: 33%, placebo: 15.6%; p=0.0214 and 0.016, respectively).Ezogabine 600mg/day did not reach statistical significance for either endpoint.

Two additional placebo controlled efficacy trials were also evaluated for drug approval (RESTORE 1 and RESTORE 2). RESTORE 1 was a 18-week study. Participants taking ezogabine 1200mg/day demonstrated a significant improvement in reduction in seizure frequency compared to placebo (-44.3% vs. -17.5%, p<0.001) and a greater responder rate (44.4% vs. 17.8%, RR 2.5; 95% CI 1.7 to 3.8, p<0.001). There was no significant difference in the proportion of patients who were seizure free. In this study, there was an unequal distribution in the two groups regarding percentage of patients on 1, 2, or 3 concurrent AEDs. RESTORE 2 was a 16 week study. Ezogabine 600mg/day and 900mg/day were shown to significantly improve the change in partial seizure frequency compared to placebo (-27.9% vs. -39.9% vs. -15.9%, for 600mg/day, 900mg, and placebo; p<0.007 and <0.001 respectively). Both doses also demonstrated a significant increase in responder rate compared to placebo (600mg/day 32% vs. placebo 17%, RR 1.9; 95% CI 1.2-2.9, p=0.002 and 900mg/day 39% vs. placebo 17%, RR 2.4; 95% CI 1.7 to 3.6, p<0.001). The proportion of patients who were seizure free was not reported in RESTORE 2. **Table 1 and 2** summarize the results of the pivotal trials. The results presented in **Table 3** demonstrate the NNT for a 25-50% reduction in seizure frequency based on maintenance phase dosing of ezogabine in the pivotal trials.

Table 1: Median % decrease in 28 day seizure frequency (ezogabine vs. placebo)

Trial	600 mg	900 mg	1200mg	placebo
Porter	23.4[NS]	29.3[&]	35.2[@]	13.1
RESTORE 1	NA	NA	44.3*	17.5
RESTORE 2	27.9[#]	39.9*	NA	15.9

* p <0.001 [&] p=0.039
\# p <0.007 [@] p=0.002

Table 2: Responder Rate percentage (ezogabine vs. placebo)

Trial	600 mg	900 mg	1200 mg	placebo
Porter	23.2[NS]	31.6[&]	33[@]	15.6
RESTORE 1	NA	NA	44.4*	27
RESTORE 2	32[#]	39*	NA	17

* p <0.001 [&] p=0.021
\# p <0.002 [@] p=0.016

Table 3 NNT based on pooled data from the pivotal trials

	600 mg	900mg	1200mg
Porter		7	6
RESTORE 1			4
RESTORE 2	7	5	

All studies showed a statistically significant increase in withdrawal due to adverse events with ezogabine compared to placebo with rates of discontinuation due to adverse events ranging from 14.4% to 29.2% and appeared to be dose-related (25% across all three studies for ezogabine vs. 11% for placebo). The two studies that reported total attrition rates also demonstrated higher total dropout rates with treatment compared to placebo. The most common adverse reactions leading to withdrawal were dizziness (6%), confusional state (4%), fatigue and somnolence (3%). In the clinical trials, dizziness was reported in 23% of patients treated with ezogabine compared to 9% of patients on placebo. Confusional state, psychotic symptoms and hallucinations were reported more frequently in patients treated with ezogabine than in those treated with placebo in the clinical trials (9% of ezogabine participants experienced a confusional state versus 3% in the placebo group). Ezogabine also caused urinary retention in clinical trials. In trials, "urinary retention, urinary hesitation and dysuria were reported in 0.9%, 2.2%, and 2.3% of patients on ezogabine, respectively, and in 0.5%, 0.9%, and 0.7% of patients on placebo, respectively.

Long-term efficacy and safety of ezogabine as adjunctive therapy has been evaluated in three open-label extension (OLE) studies following the placebo-controlled, short-term studies in adult patients with partial-onset seizures (N=778). Patient retention rates after 12 months of open-label treatment were approximately 58% in the integrated analysis of the three OLE studies. Efficacy was maintained in patients who remained in the OLE studies for up to 32 months of treatment. Frequency and severity of treatment-emergent adverse events during long-term treatment with ezogabine were similar to those reported in short-term trials. The most commonly reported events in these OLE studies included somnolence, dizziness, headache, confusional state, urinary tract infection, fatigue, and tremor.

Potential Off-Label Use

Post-herpetic Neuralgia (PHN)

In a randomized, double-blind, placebo-controlled study (N=187) of ezogabine 150-900 mg/day in adults with post-herpetic neuralgia, there was no statistically significant difference in change in average pain score from baseline to the end of the Maintenance Phase between ezogabine and placebo.

Bipolar Disorder

In a small, 3-week, open-label study of ezogabine in hospitalized patients with bipolar I disorder and acute manic symptoms, 3 of 10 patients were considered responders based on a YMRS decrease of ≥50%. Overall, the mean Young Mania Rating Scale (YMRS) and Hamilton Depression (HAM-D). Rating Scale scores were not significantly different from baseline to end of study.

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• Ezogabine can cause retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss. • Some patients with retinal abnormalities have been found to have abnormal visual acuity. It is not possible to determine whether ezogabine caused this decreased visual acuity. • The rate of progression of retinal abnormalities and their reversibility are unknown. • Patients who fail to show substantial clinical benefit after adequate titration should be discontinued from ezogabine. • All patients taking ezogabine should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. Testing should include visual acuity and dilated fundus photography. • If retinal pigmentary abnormalities or vision changes are detected, ezogabine should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.
Contraindications	• None
Warnings/Precautions	• Urinary retention: Patients should be carefully monitored for urologic symptoms. • Ezogabine can cause skin discoloration: If a patient develops skin discoloration, serious consideration should be given to an alternative treatment. • Monitor for confusional state, psychotic symptoms, and hallucinations. • Monitor for dizziness and somnolence. • The QT interval should be monitored in patients taking concomitant medications known to increase the QT interval or with certain heart conditions.

Safety Considerations

- The majority of adverse events suggest that peak-dose effects strongly impact the tolerability profile of ezogabine.
- Additionally, tolerability was determined by daily dose and influenced by the titration protocols employed.
- In randomized placebo-controlled trials, the relative risk (95% CI) of the withdrawal rate for adverse events was 1.61 (1.02–2.54) for ezogabine 600 mg/day, 2.44 (1.59–3.74) for ezogabine 900 mg/day and 2.71 (1.78–4.13) for ezogabine 1200 mg/day.
- More than 60% of discontinuations occurred during forced titration; with ezogabine discontinuation in RESTORE 1 and 2 associated with dizziness (5.5%), fatigue (3.3%), somnolence (3.5%) and confusion (6.2%).

Adverse Reactions

Common adverse reactions	The most common adverse reactions (incidence ≥4% and approximately twice placebo) are dizziness, somnolence, fatigue, confusional state, vertigo, tremor, abnormal coordination, diplopia, disturbance in attention, memory impairment, asthenia, blurred vision, gait disturbance, aphasia, dysarthria, and balance disorder

Death/Serious adverse reactions	There was 1 patient death in each treatment arm of the RESTORE-1 trial.The death in the placebo arm was ruled as unrelated to treatment, whereas the death in the ezogabine arm was ruled as possibly related. This patient died from diabetic ketoacidosis and had a history of hypertensive cardiovascular disease and had fasting hyperglycemia at baseline. In RESTORE-2, 2 treatment-emergent deaths occurred that were classified as sudden unexpected death in epilepsy (SUDEP). One occurred in a patient receiving ezogabine 600 mg/d and the other occurred in a patient given placebo. A third death occurred in a patient who had been randomly assigned to receive ezogabine 900 mg/d but who had not yet received any study drug.
Discontinuations due to adverse reactions	In the three placebo-controlled trials, 25% of patients taking ezogabine discontinued treatment due to adverse reactions. The most common adverse reactions leading to withdrawal were dizziness, confusional state, fatigue and somnolence.

Drug-Drug Interactions

Ezogabine is not a substrate for the major CYP enzymes and at clinically relevant concentrations there is little or no potential to inhibit or induce the CYP enzymes or to inhibit the major renal drug transporters. The addition of ezogabine to a range of existing AEDs showed little or no effect on the AED trough concentrations apart from a 20% decrease in lamotrigine concentrations. Results from a small phase II study showed that co-administration of valproic acid and topiramate had no impact on the PK of ezogabine whereas carbamazepine and phenytoin increased the clearance of ezogabine by approximately 27% and 36%, respectively.

Ezogabine plasma levels may be reduced by concomitant administration of phenytoin or carbamazepine. An increase in dosage of ezogabine should be considered when adding phenytoin or carbamazepine.

N-acetyl metabolite of ezogabine may inhibit renal clearance of digoxin, a P-glycoprotein substrate. Monitor digoxin levels.

Risk Evaluation

As of October 25, 2014

Sentinel event advisories	• none • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	• Ezogabine may be confused with ezetimibe. • Potiga™ may be confused with Portia® • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

The FDA-approved REMS program consists of a Communication Plan and REMS assessments that the company must submit to the FDA. A Medication Guide is part of the FDA-approved product labeling, and is considered by the FDA to be necessary for safe and effective use of ezogabine. More information is available from the product Web site at http://www.potiga.com or by contacting GlaxoSmithKline by calling 1-888-825-5249.

Purpose: To increase awareness of potential serious adverse effects including urinary retention, potential for serious drug interactions, and potential for a withdrawal syndrome subsequent to chronic administration that could occur during treatment with ezogabine.

Monitoring-Cr at baseline; eye exam incl. dilated fundus photography at baseline, then q6mo; consider fluorescein angiogram, ocular coherence tomography, perimetry, electroretinogram w/ eye exam; ECG if QT prolongation risk; s/sx depression, behavior changes, suicidality

Additionally, the post marketing studies the FDA mandated at the time of approval include;

- A prospective cohort study to better define the risk of urinary retention in patients with epilepsy treated with ezogabine and how the risk may vary with demographics (e.g. age), comorbidities that influence voiding (e.g., benign prostatic hyperplasia [BPH], multiple sclerosis) and concomitant medications that may influence voiding. The study will be performed utilizing a research database to compare patients started in two cohorts, those started on ezogabine with those started on other anticonvulsants, for the incidence of urinary retention. The study will analyze approximately 2,000 to 4,000 ezogabine-exposed patients.
- An in vitro study to evaluate whether ezogabine is a substrate for major transporters in the kidney
- An in vitro study to evaluate the potential for ezogabine to inhibit CYP2B6
- An animal physical dependence study to evaluate whether chronic administration of ezogabine produces a withdrawal syndrome following drug discontinuation.
- A controlled urodynamic trial, to include adults of both sexes in a wide range of ages, including the elderly. Pre- and post-drug urodynamic measures should be carefully collected. Urodynamic measurements should include, although not necessarily be limited to, uroflowmetry, multichannel cystometry, electromyography (EMG), and subjective sensory reporting.

Dosing and Administration

Administer in 3 divided doses daily, with or without food.
• The initial dosage should be 100 mg 3 times daily (300 mg per day) for 1week.
• Titrate to maintenance dosage by increasing the dosage at weekly intervals by no more than 150 mg per day.
• Optimize effective dosage between 200 mg 3 times daily (600 mg per day) to 400 mg 3 times daily (1,200 mg per day).
• In controlled clinical trials, 400 mg 3 times daily (1,200 mg per day) showed limited improvement compared to 300 mg 3 times daily (900 mg per day) with an increase in adverse reactions and discontinuations.
• When discontinuing ezogabine, reduce the dosage gradually over a period of at least 3 weeks

Special Populations (Adults)

	Comments
Elderly	• Partial-onset seizures, adjunct: Oral: Initial: 50 mg 3 times daily; may increase at weekly intervals in increments of ≤150 mg daily to a maximum daily dose of 750 mg daily. Note: If there is no substantial benefit after adequate titration, then discontinue use and consider other treatment options. • Use caution in elderly due to potential for urinary retention, particularly in older men with symptomatic benign prostatic hyperplasia or receive concomitant anticholinergic drugs due to a risk of urinary retention. • Systemic exposure is increased in the elderly; dosage adjustment is recommended in patients ≥65 years of age
Pregnancy	• No data identified.
Lactation	• No data identified.
Renal Impairment	• CrCl ≥50 mL/minute: No dosage adjustment necessary. • CrCl <50 mL/minute: Initial: 50 mg 3 times daily; may increase at weekly intervals in increments of ≤150 mg daily to a maximum daily dose of 600 mg daily. • ESRD requiring hemodialysis: Initial: 50 mg 3 times daily; may increase at weekly intervals in increments of ≤150 mg daily to a maximum daily dose of 600 mg daily.If no data in package insert,

	state "No data identified."
Hepatic Impairment	• Mild impairment (Child-Pugh ≤7): No dosage adjustment necessary. • Moderate impairment (Child-Pugh 7-9): Initial: 50 mg 3 times daily; may increase at weekly intervals in increments of ≤150 mg daily to a maximum daily dose of 750 mg daily. • Severe impairment (Child-Pugh >9): Initial: 50 mg 3 times daily; may increase at weekly intervals in increment of ≤150 mg daily to a maximum daily dose of 600 mg daily.
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- Epilepsy is a common neurological disorder characterized by recurring epileptic seizures. Antiepileptic drugs (AEDs) to prevent recurrence of seizures are the mainstay of treatment. There are between 16 and 51 cases of new-onset epilepsy per 100,000 people every year and over a lifetime, approximately 10 percent of people in the United States will suffer a seizure. Patients are commonly initiated on monotherapy however; many will become refractory to this medication. It is estimated that up to 22.5% of patients have drug-resistant epilepsy.
- In FY13, there were 107,475 unique patients with a diagnosis of epilepsy or seizures seen in the VA.
- NICE updated the 2004 guideline on the management of the epilepsies in adults and children with regard to drug management (January 2012). A literature search was performed and updated at 6 weeks before the end of guideline development. The evidence for outcomes were assessed for quality and presented using an adaption of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) toolbox. The majority of the new recommendations are based on moderate to very low quality evidence from randomized controlled trials and the opinion of the guideline development group. General and new 2012 recommendations were:
  - It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the child, young person or adult, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.
  - If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly.
- A recent AHRQ comparative effectiveness review was prepared to examine the comparative efficacy, safety, and tolerability of the newer versus older and innovator versus generic AEDs. Newer versus older comparisons were largely limited to studies using carbamazepine or valproic acid and to a lesser extent phenytoin and sustained/controlled-release carbamazepine. Comparisons versus clonazepam, phenobarbital, ethosuximide, or primidone were very limited or not conducted at all. Newer versus older comparisons were also largely limited to gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin. Comparisons versus felbamate, lacosamide, pregabalin, tiagabine, and zonisamide were very limited or not conducted at all.
- Ezogabine carries a black box warning for retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss. Additionally, there are significant safety concerns with ezogabine use and urinary retention, skin discoloration: confusional state, psychotic symptoms and hallucinations. And potential increases in the QT interval. Before patients are initiated on ezogabine therapy a thorough evaluation of the risk: benefit ratio for individual patients must be reviewed.

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